DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

JAN 5 2006

WARNING LETTER

VIA FEDERAL EXPRESS

Paolo Pirazzoli
Monitor Division Director
Gambro Dasco S.p.A.
Via Modenese 30
Medolla, Italy

Dear Mr. Pirazzoli:

During an inspection of your firm located in Via Modenese 30, Medolla, Italy, on September 19 through September 29, 2005, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures electromechanical dialysis control systems for standard and critical care. These products are devices within the meaning of section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 321(h)).

This inspection revealed that these devices appear to be adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (CFR), Part 820. Significant violations include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures for implementing corrective and preventive action, including failure to adequately identify the actions needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3).

   For example, review of the Design History File (DHF) for the Prisma software revision [redacted] revealed the lack of corrective action taken to address the Prisma units containing the old scales with software revision [redacted]. Prisma Service Newsletter, [redacted], dated September 22, 2001, requested "Immediate Action" to upgrade all units with software revision [redacted] with new scales. However, your firm only recommended upgrade to version [redacted] they did not require this upgrade. In addition, your firm's failure investigation found that on average the Prisma units

containing software revision [redacted], which were equipped with the old scales, cannot meet product specification (i.e., accuracy for the patient fluid removal rate of [redacted]).

Your response to FDA Observation #1, dated October 24, 2005, is not adequate. Your response states "New scales for the Prisma device were introduced in May 2003 via [redacted] because the old scales were no longer available from the supplier". This is in contrast to your firm's November 11, 2001, Risk Analysis, which specifically states new scales were introduced on the Prisma starting from May 2001 with the [redacted]

Your Risk Analysis states "The laboratory investigation demonstrated that the display accuracy issue was due to the characteristics of the new scale electronics and the problem did not occur with the old scale and the [redacted]. Based on this result, your firm decided that a mandatory rebuilding order for the Prisma devices equipped with the old scales and the [redacted] was not necessary because these devices operated within specification." The above underlined statement is contrary to other evidence. As documented by evidence collected, the Prisma devices equipped with the old scales and the [redacted] software version cannot operate within their product specification. The failure investigation shows that on average, the Prisma unit containing software version [redacted] equipped with the old scales would not meet product specification (that is the accuracy for the patient fluid removal rate of ±[redacted]).

Your response states: "Gambro Dasco will issue a rebuilding order (software upgrade to revision [redacted] on a next call basis), for the Prisma devices equipped with the revision [redacted] and [redacted]" The rebuilding order should be accomplished as a recall (through FDA) and not on a next call basis.

Your firm still does not acknowledge that the Prisma units containing software revision [redacted] equipped with the old scales fails to meet product specification based on your laboratory investigation. As such, your firm has failed to provide an explanation or further investigation for the shortcoming.

Lastly, your firm stated they will re-evaluate their Corrective and Preventive Action (CAPA) procedure, Quality System Procedure [redacted], to ensure future corrective actions include all measures to prevent the recurrence of nonconforming products and other quality problems. Your firm stated that a copy will be mailed to FDA by December 31, 2005. However, to date your firm has

provided no documentation regarding the evaluation or any revisions to the corrective action procedures.

2. Failure to establish and maintain adequate procedures for implementing corrective and preventive action, including verifying or validating the corrective and preventive action to ensure that such action is effective, as required by 21 CFR 820.100(a)(4).

   For example, there is no documented verification and/or validation on the warning statement determining the number of specific conditions of repetitive "Incorrect Weight Change Detected" alarms. This warning statement was placed on currently used Prisma machines as a result of FDA recall #Z-0456-2. In addition, there is no validation that the corrective action (i.e., adding an addendum to the Operator's Manual) was effective.

   Your response to FDA 483 Observation #2a, dated October 24, 2005, is not adequate. Your firm has yet to address the number and specific conditions of "INCORRECT WEIGHT CHANGE DETECTED" alarms which might lead to patient injury or death. Your response states "Gambro Dasco's investigation determined that these weight discrepancy alarms could be caused by a transient condition, such as bumping or moving the machine, which causes the bags to swing, malfunction of the machine, bags not hanging freely, foreign objects interfering with the scales, or blockage of flow (e.g., because of clamped lines or improperly spiked bags)." However, there was no actual investigation; the "transient condition" examples listed above are just the possible causes already listed in the Prisma Operator's Manual.

   Also, the response states "While a specific root cause of the weight alarms was not identified in several cases, functional testing of machines in the field reported as a part of the complaint investigations consistently showed [redacted]." In item 8 of this letter FDA has determined your firm has inadequate procedures for investigating complaints of device failure. This includes inadequate methodology for functional testing of machines in the user facility where the failure occurred. These inadequate procedures may hinder the determination of the root cause of excessive fluid removal.

   Two memos written in November 2005 by Gambro US to Gambro's Technical Service group regarding training to cover product service documentation, using procedure [redacted] were included in the response.

Dasco Operating Procedure (DOP) [redacted] states that your firm is to use the [redacted]). However, it goes on to say: "Unless requested by the business, service documentation may not be completed for...equipment designated in a clinic as "Removed from Service".

It would seem that there is a very real possibility that in some instances the equipment was removed from service due to a product problem. This procedure seems to allow for no documentation of these problems.

In addition, page [redacted] of [redacted] defines Routine Service Events as [redacted]". No further explanation is given.

3. Failure to establish and maintain adequate procedures for validating the device design to ensure that devices conform to user needs and intended uses, to include software validation, as required by 21 CFR 820.30(g).

   Specifically, your firm was unable to produce an adequate software validation for the original software and subsequent revisions. For example,

   a) The Design History File (DHF) for software revision [redacted] does not contain all the design inputs, including the system and software requirements for the Prisma device. There is no documentation to show how the accuracy for the patient fluid removal rate of [redacted] is met. This product specification was not translated into software requirements where the specification can be verified. Your firm failed to make this change in specification in any of its product labeling or promotional literature.

   b) The software requirements for the Prisma are incomplete in that the control and protective systems including various alarm conditions are not fully defined. In addition, your firm failed to modify the software in any way to notify the health care providers about the number of alarms per hour, or to shut down the Prisma system if the maximum of [redacted] is reached.

Your response to FDA 483 Observation #3, dated October 24, 2005, is not adequate. The correction to the item hinges on the outcome of the activities your firm had promised to perform. However, the design software activities will not be completed until May 2006. From your firm's response, it appears that your firm is planning on establishing the system and software requirements to fit software [redacted] Your firm has yet

to discuss the need for revalidating all of the software with respect to old and new relevant aspects of the design input.

In addition, your firm has yet to address the use of MDRs, complaints, service reports, and human factor study as relevant aspects to be included as part of the design input for the software validation and design validation.

4. Failure to establish and maintain adequate procedures for verifying the device design and to confirm that the design output meets the design input requirements, as required by 21.CFR 820.30(f).

Specifically, the verification data for software [redacted] shows [redacted] out of the [redacted] tests failed the new product specification of [redacted] on patient fluid removal with an allowable maximum number of [redacted] Neither the previous fluid balance specification ([redacted] hours) nor the modified fluid balance specification [redacted] with an allowed [redacted]) have been directly implemented into the software requirements for the Prisma.

Your response to FDA 483 Observation #4, dated October 24, 2005, is not adequate. Your firm's response states "Twenty pump stops was identified as a rare, but possible, worst case condition for the system." There is no documentation to show that twenty pump stops is the worst case condition for the system. In addition, an email collected by the Investigator's from [redacted] titled: Prisma Alarms, stated "[redacted]

In addition, your response states: "Investigation has determined that the [redacted]. The fact that some alarms were not expected to meet the delivery accuracy requirement was specified, but the explicit list of alarms included in each category was not documented in the specification."

No investigation was provided. What is the unclear, incomplete specification? Which alarms would be included in the explicit list of alarms for each alarm category?

5. Failure to establish and maintain adequate procedures for identification, documentation, validation or where appropriate verification, review and approval of design changes before implementation, as required by 21 CFR 820.30(i).

   Specifically, review of the validation records for Prisma System software revision [redacted] found:

   - Inadequate testing of the software revision [redacted]
   - Failure to establish a protocol for the clinical evaluation testing of software revision [redacted]
   - Failure to adequately document why the clinical trial for software revision [redacted] was performed on old scales; and not performed on the new scales, when the software revision was only mandated for new scales.

   Your response to FDA 483 Observation #5a, dated October 24, 2005, is not adequate. Your firm's response states that they will start reviewing and revising their Quality System procedures, [redacted] dealing with the identification of the proper level of testing depending on the extent of the software changes on October 24, 2005. Your firm stated that they anticipate this testing to be completed by the end of March 2006, however, your firm did not provide the revised procedures and evidence of their implementation nor has the software been adequately validated or revalidated.

   Your response to FDA 483 Observation #5b, dated October 24, 2005, is not adequate. Your firm states that [redacted] agreed to perform some simulations of treatment in the MFG GAMBRO Dasco division with the Prisma equipment rev. [redacted]. These simulations were to verify if during the performance of the tests, the practice, which is normally used in the hospital, differs significantly from the methods foreseen for the performance of the in-vitro tests. Furthermore, it states that [redacted] confirmed that the tests foreseen by the test protocol for the in-vitro verification and validation are found to also cover the simulations of anomalies that can occur in the clinical environment.

   Your firm failed to establish a protocol for the clinical evaluation and in-vitro testing for software revision [redacted] conducted by [redacted]. No protocol was included in the response. In addition, there is no report written by [redacted] documenting his observations, evaluations, and conclusions.

Your response to FDA 483 Observation #5c-d, dated October 24, 2005, is not adequate. Your firm states they will revise Quality System Procedure [redacted]" to (1) describe when a clinical evaluation protocol is needed; (2) detail the purpose of the clinical evaluation; and (3) define the templates to be used to collect data. Your firm stated that document [redacted] is expected to be completed by the end of March 2006. However, your firm provided no documentation in support of their corrective actions.

6. Failure to establish and maintain adequate procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria, as required by 21 CFR 820.80(d).

   Specifically,

   a) Four batches (Lot numbers [redacted] and [redacted] of HDBM Phoenix EPROMS devices ([redacted] labeled as containing operating software version [redacted] were released and distributed to the field, although, each batch contained software version [redacted], which was not a released/approved software version. The firm had received at least 24 complaints in 2005 relating to this problem.

   b) Blank, ready-for-use certificates of conformance forms, required for the release of the Prisma and Prismaflex devices, contain pre-printed "OK" designations for three of the release criteria.

   c) Review of 30 Prismaflex Device History Records (DHR) revealed 2 units, [redacted], were released and shipped although information required for release was missing (i.e., hour meter reading and approval/review signature by Production Quality (PQ)).

   d) Review of 15 Phoenix systems DHRs, recently released, revealed that a few DHRs ([redacted]) contained conflicting information regarding the number and type of failures encountered during production.

   Your response to FDA 483 Observation #6a, dated October 24, 2005, is not adequate. Your firm promised to (1) restrict all old master copies of EPROMs in a dedicated area; (2) clarify procedure [redacted] through better controls and retraining; and (3) update procedure [redacted] requiring the checksum value to be recorded in the DHR of the produced spares. It could not be determined if your firm was going to review and address the 24 complaints received in 2005.

Your response to FDA 483 Observation #6b, dated October 24, 2005, appears to be adequate. Your firm opened a CAPA ([redacted]), dated September 30, 2005, to identify the root cause of this issue on September 30, 2005 and found that the forms were electronically pre-printed. The document has been updated and the employees have been retrained.

Your response to FDA 483 Observation #6c, dated October 24, 2005, is not adequate. Your firm opened a CAPA ([redacted], dated September 30, 2005, and found that the manufacturing and production quality personnel had not been properly trained. A process risk analysis for product release will be conducted along with the validation activities. These are expected to be completed November 30, 2005. However, your firm provided no documentation in support of your corrective actions. The product release validation audit, done only on monitors and immediately after the training, is not necessarily an indication that product release mechanisms are in compliance. In addition, the validation does not address the inadequate release of components such as EPROMs and rework/repair kits, which was an issue during the inspection and also show up on their complaint databases as out of box failures.

Your response to FDA 483 Observation #6d, dated October 24, 2005, is not adequate. Your firm opened a CAPA ([redacted]), dated September 30, 2005, and found that personnel had not been properly trained on the procedure for troubleshooting and the requirement to link the list of intervention in the Final Testing Data Record with the failures in the troubleshooting module. The process improvement and validation activities are expected to be completed by December 2005. These were not included in the October 24, 2005, response.

7. Failure to establish and maintain instructions and procedures to ensure that service reports that represent an event which must be reported to FDA under 21 CFR 803 or 804 shall automatically be considered a complaint and shall be processed in accordance with the requirements of 820.198, as required by 21 CFR 820.200.

   For example, review of your firm's 2003 to 2005 service database found approximately 99 Prisma service reports relating to fluid removal events that represent possible MDR reportable events which were not considered as complaints.

   Some examples,

	Work Order #	Date Arrived	Reported Condition
2005	[redacted]	August 10, 2005	Staff reports inaccurate fluid removal.
	[redacted]	July 16, 2005	Pulling too much weight.
	[redacted]	March 9, 2005	Patient fluid removal rate set for 90 ml/hr but machine pulled 1920 ml/hr.
	[redacted]	February 22, 2005	Removal 150mm greater than set weight.
2004	[redacted]	December 29, 2004	Machine malfunction. Removed twice amount of fluid requested.
	[redacted]	December 18, 2004	Machine is taking off fluid when zero is entered.
	[redacted]	July 21, 2004	Take off too much weight.
	[redacted]	February 23, 2004	Weight removal is inaccurate.
2003	[redacted]	November 25, 2003	Machine pulls off too much fluid.
	[redacted]	October 1, 2003	Pump Noisy. Machine pulled 800ml when set for 300ml.
	[redacted]	April 1, 2003	Machine Removed 311cc of fluid when set for 0 fluid removal.
	[redacted]	January 9, 2003	Set for 50cc's and removing 800cc's.

Your response to FDA 483 Observation #7, dated October 24, 2005, is not adequate. Your firm states that they would perform a review of all Prisma service reports since 2002 and reassess their MDR applicability. However, there is no indication that this would be done for the Prismaflex or the Phoenix, in which the EIR shows that many complaints that appear to be MDR reportable. Review of Attachment #7-3, which addresses the analysis of [redacted] reveals it only applies to US data. There is no indication that the data for foreign quality and service will be analyzed.

8. Failure to establish and maintain adequate procedures to investigate the cause of nonconformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(2).

   Specifically, there were inadequate failure investigation procedures to review, evaluate and investigate complaints involving possible failure of a device or labeling to meet any of its specifications with respect to the Prisma fluid removal. The procedures did not adequately address how

valuable information, such as that listed below, should be obtained or collected, to the extent possible, in order to make an adequate failure investigation and conclusion:

a) Collecting and documenting treatment history data when available.

b) Collecting and documenting I/O (input and output volumes during a treatment) history including the I/O of the time period(s) in question when available.

c) The methodology used in identifying the failure mode(s) and/or mechanism(s) along with the associated component(s) involved.

d) The methodology including the tools/equipment/supplies used to perform the simulated run (to verify machine functionality and accuracy).

Your response to FDA 483 Observation #8, dated October 24, 2005, is not adequate. Your firm promised to develop a new checklist to ensure a consistent failure investigation approach for significant complaints. However, your firm provided no documentation in support of the corrective actions. In addition, your firm's response does not clearly define, nor give a rationale for, what Gambro feels are "most significant complaints", nor does it provide any of the checklists referred to in the response.

9. Failure to establish and maintain adequate procedures for receiving, reviewing and evaluating complaints by a formally designated unit and to evaluate complaints to determine if they represent an event which is required to be reported to FDA under Part 803 Medical Device Reporting, as required by 21 CFR 820.198.

Specifically:

a) Your firm failed to follow the Gambro Dasco procedure, [redacted], for reporting repair codes [redacted]) and [redacted]) as complaints. In addition, your complaint forms lack information required per your firm's procedures such as device serial number, incident date, software revision, hours on the device, reporting hospital, clinical consequence, etc.

Your response to FDA 483 Observation #9, dated October 24, 2005, is not adequate. Your firm stated that there was an incorrect interpretation of [redacted] procedure [redacted]

[redacted] and that a revised procedure will treat out-of-box failures as complaints. In addition, your firm stated that they will revise their Complaint Handling procedure, [redacted] to capture all required information. However, your firm provided no documentation in support of the corrective actions. In addition, review of Attachment #9 - a1 shows the procedure that is included is Revision 2, whereas, this same procedure was included in Attachment #7 – 3, however as revision 3.

Review of Attachment #9-b1, which contains your firm's new complaint handling procedures, reveals:

- Page 4 of the complaint handling procedure states that: "...expressions of dissatisfaction...consequent to normal wear and tear of the device are not considered as complaints". It is not clear what is meant by "expressions of dissatisfaction".

- Your firm continues to have, and refer to the use of, more than one complaint form [redacted]. It is still difficult to ascertain how these will be used and which is the primary form for documenting and processing complaints.

- The procedure clearly shows Gambro is most concerned with class [redacted] complaints concerning patient or user safety, i.e. MDR, and seems to minimize class [redacted] complaints. However, the possibility that some class [redacted] complaints (for example "products not meeting specifications") could potentially be MDR, seems to be overlooked, or at least not addressed.

- Page [redacted] of the complaint procedure refers to complaints "...between class [redacted] and [redacted]." There is no provision for, or definition of the meaning of "between".

- Your firm continues to allow more than one complaint/event to be covered by just one complaint ID number. The trending of the numbers and types of complaints can be skewed by this process.

- The definition of class [redacted] complaints allows for the inclusion of reports of logistics/shipping issues. Shipping/logistical issues and complaints should be assigned a separate classification in order to avoid confusion.

b) Your firm failed to conduct adequate investigations of complaints, from 2002 to 2005, containing information that the Prisma device may have caused or contributed to a death or serious injury. As a result these

incidents were not reported to FDA under 21 CFR 803. For example:

Complaint #	Type of Event	Date Received	Event Description
[redacted]	Death (US)	November 26, 2004	Air in blood.
[redacted]	Death (US)	June 10, 2004	Pulled 2 liters too much. Patient may die – med intervention. On Sunday, June 6, patient died.

Your response to FDA 483 Observation #10, dated October 24, 2005, is not adequate. Your firm stated that they will perform a retrospective review of the non US Prisma complaint files for calendar years 2002-2005 with the support of an intensive care physician. Your firm stated that they will file any retrospective MDRs to FDA by November 30, 2005. There was no evidence of this review provided to date. The response states your firm would perform a review of all non US Prisma complaints (not service reports) since 2002 and re-assess their MDR applicability. There is no indication that this would be done for the Prismaflex or the Phoenix, which the EIR shows that many complaints appear to be MDR reportable. Your firm stated that the retrospective review will not include any complaints related to fluid removal because you believe that it is unnecessary to submit a retrospective MDR for each unexpected fluid loss or gain that occurred in the past. This is because your firm believes that the corrective action (worldwide safety alert, FDA Recall #Z-1545-05) properly corrects the conditions that trigger a weight balance alarm. Your firm also stated that they will revise their MDR procedure to ensure that: (1) the decision for deciding whether the complaint is an MDR-reportable event and the date of the event is documented on the complaint form; and (2) all decisions regarding whether the complaint is an MDR-reportable event are supported by the MDR checklist. However, your firm provided no documentation to show that MDRs have been submitted to FDA or that the MDR procedure has been updated and implemented. In addition, your firm needs to perform a retrospective review of all complaints, including complaints related to fluid removal, to determine if they should be submitted as MDRs.

10. Failure to establish and maintain adequate procedures for implementing corrective and preventive action. These procedures shall include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems, as required by 21 CFR 820.100(a)(1).

Specifically, [redacted] reports, intended to provide field experience data for review and trending:

a) do not include the Prismaflex device
b) include only US field experience and not the rest of the world field experience
d) count multiple alarms as only one failure

Your response to FDA 483 Observation #11 (a-b), dated October 24, 2005, is not adequate. For Observation 11a, your firm stated that their next [redacted] report will include the Prismaflex US Service Reports. However, no documentation was submitted in support of this corrective action. For Observation #11b, your firm stated that you will initiate a global sales study to include all markets where a Gambro service organization is active to assess the feasibility of receiving Gambro Dasco service reports for countries currently not included. However, your firm provided no documentation in support of their corrective actions.

For Observation #11d, your firm stated that a single component failure may generate multiple alarms and that the [redacted] system is designed to track specific failures, not the number of alarms generated by the machine. Your firm's response appears to be adequate.

11. Failure to submit a premarket notification submission to the Food and Drug Administration when a change or modification in the device that could significantly affect the safety or effectiveness, e.g. significant change or modification in design, material , chemical composition, energy source, or manufacturing process, as required by 21 CFR 807.81(a)(3)(i).

Specifically, your firm did not submit a premarket notification submission, 510(k), for the Prisma [redacted] The revision changed the product specifications by adding the maximum number of [redacted]

Your firm did not specifically respond to this comment in their October 24, 2005 response.

Additionally, the above-stated inspection revealed that your devices are misbranded under section 502(t)(2) of the Act, in that your firm failed or refused to furnish any material or information required by or under section 519 respecting the device and 21 CFR Part 803 Medical Device Reporting (MDR) regulation and 21 CFR Part 806 Reports of Corrections and Removals.

Significant violations include, but are not limited to, the following:

1. Failure to submit reports to FDA after receiving information that reasonably suggested that one of your marketed devices may have caused or contributed to a death or serious injury, as required by 21 CFR 803.50(a)(1).

   For example:

   a) A patient died on June 6, 2004, two days after the Prisma removed 100 cc too much fluid from the patient. This event should be reported as a device-related death. (Gambro Dasco complaint #[redacted] – Gambro Renal Products complaint #[redacted].

   b) A facility reported that a Prisma contributed to the death of a patient on November 20, 2004, after multiple alarms for air in the blood and a blood leak. This event should be reported as a device-related death. (Gambro Dasco complaint #[redacted] - Gambro Renal Products complaint #[redacted].

   c) A hospital reported an incident in December 2003 where a Prisma alarmed for incorrect replacement weight change and could not be cleared. The Prisma pulled off fluid when not programmed to do so and there was a subsequent drop in the patient's blood pressure. This event should be reported as a life-threatening serious injury. (Gambro Dasco complaint #[redacted] - Gambro Renal Products complaint #[redacted]

   d) Over a three hour period on September 17, 2004, a Prisma took off 100 ccs of fluid more than the removal rate that was set on the machine (removed 258 cc/hr when set 200 cc/hr, removed 334 cc/hr when set 250 cc/hr, and removed 329 cc/hr when set 150 cc/hr) and the treatment was stopped. The patient was hypotensive and given intravenous fluid. This event should be reported as a life-threatening serious injury. (Gambro Dasco complaint #[redacted] - Gambro Renal Products complaint #[redacted].

   e) On December 29, 2004, a Prisma removed too much fluid (the actual patient fluid removal was 812 ml/hr when set at 150 ml/hr and 722 ml/hr when set at 100 ml/hr). This event should be reported as a life-threatening serious injury. (Gambro Dasco complaint #[redacted] - Gambro Renal Products complaint #[redacted].

f) A report that a Prisma removed too much fluid from a patient on February 24, 2003, (set for 300 cc/hr, but removed 704 cc in one hour). The machine continued to remove fluid after they decreased the rate to zero cc/hr, so they disconnected it. This event should be reported as a life-threatening serious injury. (Gambro Dasco complaint #[redacted] - Gambro Renal Products complaint [redacted]).

g) A report that a Prisma removed 655 cc too much fluid from a critical care patient in less than two hours on July 26, 2002. This event should be reported as a life-threatening serious injury. (Gambro Dasco complaint #[redacted] - Gambro Renal Products complaint #[redacted].

h) A report that the Prisma dialysate pump was above the limit and almost dehydrated a baby on March 17, 2002. This event should be reported as a life-threatening serious injury. (Gambro Dasco #[redacted] - Gambro Renal Products #[redacted]).

i) A service report received March 9, 2005 that the patient fluid removal rate set for 90 ml/hr, but the Prisma machine pulled 1920 ml/hr. This event should be reported as a life-threatening serious injury. (Gambro Dasco service record #[redacted] - Gambro Renal Products service record #[redacted]).

j) A service report received October 1, 2003 that the Prisma machine pulled 800 ml of fluid when set for 300 ml. This event should be reported as a life-threatening serious injury. (Gambro Dasco service record #[redacted] - Gambro Renal Products service record #[redacted]).

k) A service report received January 9, 2003 that a Prisma machine set for 50 ccs was removing 800 ccs. This event should be reported as a life-threatening serious injury. (Gambro Dasco service record #[redacted] - Gambro Renal Products service record #[redacted].

l) A service report received September 2, 2005 that a Prisma pulled off too much fluid (set for 300 cc and removed 800 cc). This event should be reported as a life-threatening serious injury. (Gambro Dasco #[redacted].

m) A service report received May 19, 2004 that a Prisma set for 130 ml/hr removed 627 in one hour and 320 the next hour. This event should be reported as a life-threatening serious injury. (Gambro Dasco #[redacted]).

2. Failure to submit reports to FDA after receiving information that reasonably suggested that one of your marketed devices has malfunctioned, and such device would be likely to cause or contribute to a death or serious injury if the malfunction were to recur, as required by 21 CFR 803.50(a)(2). For example,

   a) A Prisma removed too much fluid from a patient on October 22, 2003 (the machine was set for patient removal of 300 ml/hr, but removed 513 ml/hr for one hour, then removed 501 ml/hr the next hour). This event concerns a device malfunction that may also have contributed to a serious injury. The event should be reported at the minimum as a malfunction. (Gambro Dasco complaint #[redacted]- Gambro Renal Products complaint #[redacted]).

   b) On July 28, 2003, a Prisma removed excess fluid from a patient (200 cc of patient fluid removed when set at zero). This event concerns a device malfunction that may also have contributed to a serious injury. The event should be reported at the minimum as a malfunction. (Gambro Dasco complaint #[redacted]- Gambro Renal Products complaint #[redacted].

   c) A Prisma removed too much fluid during one hour of treatment on June 4, 2003 (set for 170 cc/hr and removed 490 cc in one hour). This event concerns a device malfunction that may also have contributed to a serious injury. The event should be reported at the minimum as a malfunction. (Gambro Dasco #[redacted]- Gambro Renal Products complaint #[redacted].

   d) A report that a patient lost an unknown amount of blood due to a tear in the blood pump segment on May 20, 2004. This event concerns a device malfunction that may also have contributed to a serious injury. The event should be reported at the minimum as a malfunction. (Gambro Dasco complaint #[redacted] - Gambro Renal Products complaint #[redacted]. [A similar report of a hole in blood pump tubing on May 17, 2004 where the patient's blood pressure dropped and the patient was given one unit of blood was reported by Gambro Dasco as a serious injury under [redacted]

   e) A report that a split in the pump segment caused undetermined blood loss on May 9, 2005. This event concerns a device malfunction that may also have contributed to a serious injury. The event should be reported at the minimum as a malfunction. (Gambro Dasco complaint #[redacted]- Gambro Renal Products complaint #[redacted]).

f) A report from France that on December 1, 2003 during treatment with a Prisma, the pumps suddenly turned more rapidly and patient fluid removal was much higher than scheduled, with no alarms. (Patient removal set zero, but was 358 grams). (Gambro Dasco complaint #[redacted]).

g) A report from France that in November or December 2003 while children were being treated, fluid removal was not what was scheduled. Loss was too high. Staff notices such problems when arterial pressure falls or the nurse checks the input/output data display (every hour). (Gambro Dasco complaint #[redacted]

h) A report from France that on May 4, 2003, after 12 hours treatment, the patient display was four times higher than scheduled. Pumps were turning very high speed. No alarms were triggered. Treatment was stopped. (Gambro Dasco complaint #[redacted]).

i) A report from France that on September 4, 2001, a Prisma was used to treat a 25 kg child with patient fluid removal set at 200 ml/hr. After three hours, the actual weight loss was 600 grams but the Prisma status screen displayed only 233 ml patient fluid removed. The file noted that this event was a near incident vigilance report and an MDR malfunction would be filed. There was no copy of a Vigilance or MDR report in the file. (Gambro Dasco complaint #[redacted]).

3. Failure to submit a baseline report on FDA Form 3417, or electronic equivalent as approved by FDA under 803.14 for a device when the device model is first reported under 803.50, as required by 21 CFR 803.55.

   Specifically, the Prismaflex 510(k) ([redacted] letter was issued on October 2004 and the MDR baseline report adding the Prismaflex was not conducted until July 2005.

   Your firm did not specifically respond to this comment in their October 24, 2005 response.

4. Failure to submit a written corrections and removals report to FDA of any correction or removal of a device initiated by such manufacturer or importer if the correction or removal was initiated to reduce a risk to health posed by the device, as required by 21 CFR 806.10(a)(1).

   Specifically, your firm made several corrections and removals without notifying FDA. Some examples for the Prisma device include:

- January 10, 2003 - [redacted] Addendum/modification to Prisma manual to clarify details of the consequences of repetitive overrides of the "Incorrect Weight Change Detected" alarm.

- August 6, 2002 [redacted] - Service and Operators and Service Manuals modified with ECG artifact warnings, new software revisions, and modifications of jumpers.

- December 10, 2001 - [redacted] – The initial notice memo is dated December 10, 2001, but the final released notice is dated December 13, 2001. It alerts of artifacts appearing on ECG screens and cardiac monitors when used with the Prisma as a result of electrical interference caused by a peristaltic pump in the Prisma. Gambro felt the artifacts could be misinterpreted as cardiac emergencies. Note: Gambro provided a warning label for the front of the Prisma and an addendum to the operator's manual.

- January 16, 2001 - Recommended Field Action - possibility of air bubbles larger than 10 ul (up to 100 ul) passing by the UABD (unintended air in blood detector) and not being detected. Recommend redesign of component and retrofit.

- December 18, 2000 - [redacted] – Announces a new Warning Label to be put on the effluent scale "to recommend safer machine usage."

- September 27, 2000 - [redacted] - To announce the improvement of the UABD to prevent false alarms. This would require retrofits of unit in the field.

Some examples for the Prismaflex device include:

- April 29, 2005 [redacted] - Two weeks after the release of version [redacted] the cover letter to this notice, and the notice indicate that Gambro had become aware of "Communication errors" when using software version [redacted]. The Notice states that this error would cause the [redacted]" and that the [redacted]. However, the letter then states that under these conditions the machine [redacted] and that [redacted]"

- December 10, 2004 [redacted] - Issued just after the 510k approval, this announces the release of software version [redacted], intended to correct many device performance issues found in the original software release of [redacted] These included:
    - correcting an unspecified "flow rate bug";
    - the addition of new alarms;
    - reducing (not eliminating) the possibility of unintentional unloading of the disposable set, allowing blood to enter into the fluid bags;
    - reducing (not eliminating) the possibility for a fluid bag to empty without an EMPTY BAG alarm; and
    - reducing (not eliminating) the possibility of false air in blood/ no line in air detector and malfunction ABD alarms.

Some examples for the Phoenix device include:

- March 14, 2005 - [redacted] announces new operator's manuals for the Innova (same as the Phoenix), described in the previous [redacted] dated February 15, 2005. The new manuals were due in part to cases of reported chemical hemolysis.

- February 16, 2005 - [redacted] - This announces the release of software version [redacted] to correct anomalies in previous version [redacted]. Some of the anomalies listed as being corrected included but were not limited to:
    - eliminate occurrences of the machine switching back to rinseback phase during treatment; NOTE: identified by the firm as Class [redacted] (= potentially safety relevant)";
    - correction of inaccurate liters processed; NOTE: identified by the firm as Class [redacted] (= potentially safety relevant)";
    - "correction to avoid system crash";
    - the unintended reset of the "Fluid Removed" and "Liters Processed" parameters;
    - the "wrong" visualization of the Washback Volume;
    - the "wrong" K_FM calculation during calibration phase;
    - eliminating the reset of total heparin parameter after power failure; and
    - eliminate the loss of BPM values.

- July 23, 2004 [redacted] - This announces the availability of software revision [redacted]. Note: This newsletter indicates some "bugs" were being corrected, and contains a list of many "known problems still existing on SW [redacted]" Many of these are the same as those indicated in the above bullet.

- February 3, 2004 - [redacted] - Replacement of flowmeters in the field. Documents included with this form indicate the replacement of the flowmeters was the result of complaints of incorrect patient fluid removal without alarms.

Your firm did not specifically respond to this comment in their October 24, 2005 response.

This letter is not intended to be an all-inclusive list of violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Given the serious nature of these violations of the Act, electromechanical dialysis control systems for standard and critical care manufactured by your firm imported or offered for import are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. § 381(a), in that they appear to be adulterated. As a result, FDA may take steps to refuse these products, known as "detained without physical examination," until these violations are corrected.

In order to remove the devices from detention, you should provide a written response to this Warning Letter as described below and correct the violations described in this letter. We will notify you if your response is adequate, and we may need to re-inspect your facility to verify that the appropriate corrections have been made. In addition, U.S. federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter, of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include all documentation of the corrective action you have taken. If you plan to make any corrections in the future, include those plans with your response to this letter as well. If the

documentation is not in English, please provide a translation to facilitate our review.

Your response should be sent to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement

A, OB/GYN, Gastroenterology and Urology Devices Branch, 2098 Gaither Road, Rockville, Maryland 20850 USA, to the attention of Paul Tilton.

If you need help in understanding the contents of this letter, please contact Paul Tilton at the above address or at (240) 276-0115 or FAX (240) 276-0114.

Sincerely yours,

Timothy A. Ulatowski
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